--34. The method of claim 4 wherein said cancer is non-small cell lung cancer.

35. The method of claim 4 wherein said cancer is pancreatic cancer.

36. The method of claim 4 wherein said cancer is bladder cancer.

37. A method for treating a cancer selected from the group consisting of breast cancer, non-small cell lung cancer, pancreatic cancer and bladder cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline derivative, to a human patient in an amount effective to treat the cancer.--

## REMARKS

### Amendments

Claims 20-33 have been cancelled, without prejudice to filing a continuing application directed thereto, in order to avoid the excess claim fee associated with the addition of claims 34-37 herein. Claims 34-37 added herein find basis in at least original claims 1, 4 and 5 and elsewhere in the specification. In that the amendments do not introduce new matter, their entry is respectfully requested.

### Request to withdraw the finality of the Office Action

Applicants respectfully request that the finality of the Office Action dated 10/25/00 be withdrawn as being premature. In particular, Applicants submit that the Office Action should not have been made final since it included new rejections, on prior art not of record (the Mosconi, Carmichael, and Clemons references), of claims amended to include limitations which should reasonably have been expected to be claimed. MPEP 706.07(a). In particular, the claims were previously amended to include the gemcitabine chemotherapeutic that was clearly supported by the specification (page 17, line 15) and thus obviate the Section 102 prior art rejections previously raised.

Applicants would appreciate it if the Examiner could call the undersigned to advise whether or not the finality of the Office Action will be withdrawn, so that they can determine whether a petition under 37 CFR §1.181 should be filed. See MPEP 706.07(c).

The Section 103 Rejections

Claims 1-9 and 12-13 are rejected under 35 USC Section 103(a) as being unpatentable over various primary references - Baselga *et al.* (1997), Norton *et al.* (1997), Lippman *et al.* US Patent No. 5,578,482, Hynes *et al.* (1994) or Arakawa *et al.* US Patent No. 5,783,186 - allegedly disclosing combining anti-HER2 antibodies with non-anthracycline chemotherapeutic agents. Since none of these references teaches combining anti-HER2 antibodies with gemcitabine, the Examiner relies on various secondary references - Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), and Carmichael *et al.* (1995) - allegedly teaching that gemcitibine looks promising, is an effective chemotherapeutic agent, is ideal for combination therapies, has a low toxicity and has a high response rate.

The Examiner concludes that it would have been *prima facie* obvious to select the specific non-anthracycline chemotherapeutic agent gemcitabine in the combination therapies of the primary references and one would have been motivated to do so because gemcitabine has low toxicity and high response rate and is ideal for combination therapy as allegedly taught by the secondary references.

Claims 1-9 are rejected under 35 USC Section 103(a) as being unpatentable over Hudziak *et al.* US Patent No. 5,770,195 in view of the above-noted secondary references - Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), and Carmichael *et al.* (1995).

Claims 1-9 and 12-13 are rejected under 35 USC 103(a) as being unpatentable over Baselga *et al.* (1996) in view of the above-noted secondary references - Clemons *et al.* (1997), Mosconi *et al.* (1997),

Carmichael *et al.* (1997), and Carmichael *et al.* (1995)., and further in view of Hynes *et al.* (1994).

Claims 1-9 and 12-33 are rejected under 35 USC Section 103(a) as being unpatentable over Baselga et al. (1996), Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), Carmichael *et al.* (1995), in view of Singal *et al.* (1995) and further in view of Seifert *et al.* (1998).

The Examiner contends that articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. The Examiner further relies on Singal *et al.* as allegedly teaching that anthracycline derivatives are known to cause severe heart failure, thereby making them less desirable than other chemotherapeutics. Seifert *et al.* is relied on as teaching the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.

The Examiner contends that it would have been *prima facie* obvious to package the reagents necessary for the method taught by Baselga *et al.*, Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), or Carmichael *et al.* (1995) into a convenient kit form, that that it would have been *prima facie* obvious to include a warning to avoid the use of an anthracycline derivative, or when they are administered to administer a cardioprotectant.

Claims 1-9 and 14-33 are rejected under 35 USC Section 103(a) as being unpatentable over Norton *et al.* (1997), Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), Carmichael *et al.* (1995), in view of Singal *et al.* (1995) and further in view of Seifert *et al.* (1998).

Claims 1-5, 7-9, 12 and 14-33 are rejected as being unpatentable over Lippman *et al.*, US Patent No. 5,578,482, Clemons *et al.* (1997),

Mosconi *et al.* (1997), Carmichael *et al.* (1997), Carmichael *et al.* (1995), in view of Singal *et al.* (1995) and further in view of Seifert *et al.* (1998).

Claims 1-5, 7-9, 12 and 14-33 are rejected as being unpatentable over Hynes *et al.* (1994), Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), Carmichael *et al.* (1995), in view of Singal *et al.* (1995) and further in view of Seifert *et al.* (1998).

Claims 1-5, 12 and 14-33 are rejected as being unpatentable over Arakawa *et al.* US Patent No. 5,783,186, Clemons *et al.* (1997), Mosconi *et al.* (1997), Carmichael *et al.* (1997), Carmichael *et al.* (1995), in view of Singal *et al.* (1995) and further in view of Seifert *et al.* (1998).

Applicants submit that the presently claimed invention is patentable over the cited art.

Claims 1 and its dependent claims pertain to a method of treating a human patient comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline antibiotic. Claims 5, and 34-36 added herein specify that the disorder to be treated is breast cancer, non-small cell lung cancer (NSCLC), pancreatic cancer or bladdér cancer. Claim 14 and the claims which depend thereon relate to the article of manufacture which can be used to perform the method of claim 1.

Applicants submit that the presently claimed methods and articles of manufacture are patentable over the cited art.

As acknowledged by the Examiner, the actual combining of an anti-ErbB2 antibody and gemcitabine to treat a disorder characterized by overexpression of ErbB2 is not described by the cited references. The present application on the other hand, discloses combining an anti-

ErbB2 antibody (such as the exemplified HERCEPTIN® antibody) and gemcitabine to treat diseases such as breast cancer, NSCLC, pancreatic cancer and bladder cancer. Subsequent human clinical data has confirmed that this is a desirable combination. See Miller *et al. Oncology* 15(2):38-40 (February, 2001) (copy attached) which describes preliminary results of a phase II human clinical trial which evaluated the presently claimed gemcitabine and anti-ErbB2 antibody combination with respect to HER2-overexpressing metastatic breast cancer. The combination is well tolerated and appears to be highly active (see abstract of Miller *et al.*). Neither significant cardiac toxicity nor clinical congestive heart failure has been reported to date (1st paragraph in column 1 on page 40 of Miller *et al.*). The lack of significant cardiac toxicity associated with the presently claimed anti-ErbB2 antibody and gemcitibine combination contrasts against the increased cardiac side-effects observed with the anti-ErbB2 antibody and anthracycline derivative combination described at page 47 of the present application.

The present invention is not limited to therapy of metastatic breast cancer. This is demonstrated by the attached abstract by Safran *et al. Proc Am. Soc. Clin. Oncol.* 20:130a (2001), which describes Phase II human clinical data in which the presently exemplified anti-ErbB2 antibody (HERCEPTIN®) is combined with gemcitabine to treat metastatic pancreatic cancer. The abstract states that "Herceptin and gemcitabine have promising activity in an important subset of patients with metastatic pancreatic cancers that overexpress HER-2/*neu*."

The presently claimed combination has further been assessed in patients with HER2 overexpressing, untreated, advanced NSCLC. See the copy of Zinner *et al. Proc. Am. Soc. Clin. Oncol.* 20:328a (2001) attached hereto. Zinner *et al.* note that the regimen is well tolerated, response rates are encouraging, and HERCEPTIN® does not alter gemcitabine clearance.

Hence, Applicants submit that the presently claimed combination of an anti-ErbB2 antibody and gemcitabine is effective and lacks the cardiac side effects associated with the anti-ErbB2 antibody and anthracycline antibiotic combination.

The Examiner has acknowledged the novelty of the presently claimed method and article of manufacture of claims 1 and 14 over the cited references. Applicants rely on unexpected results as providing objective evidence as to the patentability of the presently claimed combination. In particular, Applicants note that the combination of an anti-ErbB2 antibody (such as HERCEPTIN®) and gemcitabine has been reported to be synergistic. In particular, Nagourney *et al. Breast Cancer Res. Treat.* 57:116 (1999) attached state that Trastuzumab (the generic name for HERCEPTIN®) enhances the activity of gemcitabine. Bunn *et al.* found additive or synergistic effects between HERCEPTIN® and gemcitabine in NSCLC lines that overexpress HER-2. (No synergy or additive effects were seen with SCLC.) See Bunn *et al. Proc. Am. Assoc. Canc. Res.* 41:719 (2000). Zinner *et al.* note that HERCEPTIN® has been shown to be synergistic with cisplatin and gemcitibine in HER2 overexpressing NSCLC. While Konecny *et al.* report that gemcitabine is antagonistic with HERCEPTIN® (Konecny *et al. Breast Cancer Res. Treat.* 57:114 (1999); copy attached), these authors acknowledge that further clinical testing is warranted, and several other skilled artisans report otherwise, as noted above. Moreover, Applicants rely on the human clinical data which reveals the effectiveness and lack of significant cardiac toxicity as discussed above as providing further evidence of the unexpected desirable results associated with the presently claimed combination. Reconsideration and withdrawal of the Section 103 rejections of the pending claims is earnestly requested in view of the above.

Should the Examiner have any questions concerning the request to withdraw finality of the Office Action or this amendment, she is invited to call the undersigned at the number noted below.

Serial No.: 09/209,023

Respectfully submitted,

GENENTECH, INC.

Date: August 27, 2001

By: WMLee

Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

09157

PATENT TRADEMARK OFFICE